

CLAIMS

I claim:

1. A method of modulating angiogenesis in a mammal in need of such treatment comprising administering a therapeutically-effective amount of a composition comprising a TWEAK receptor antagonist or TWEAK receptor agonist.
2. The method of claim 1 wherein the composition further comprises a pharmaceutically acceptable carrier.
3. The method of claim 2 wherein the mammal is a human.
4. The method of claim 3 wherein the TWEAK receptor comprises a sequence selected from the group consisting of:
 - (a) amino acids 28-79 of SEQ ID NO:7; and
 - (b) naturally occurring variants of (a).
5. A method of inhibiting angiogenesis according to claim 4 wherein the composition comprises a TWEAK receptor antagonist.
6. The method of claim 5 wherein the antagonist is selected from the group consisting of soluble receptor fragments, antibodies, antisense and triple helix forming nucleic acids, peptides, and small molecules.
7. The method of claim 6 wherein the antagonist comprises a soluble TWEAK receptor fragment.
8. The method of claim 7 wherein the antagonist further comprises an Fc polypeptide or leucine zipper domain.
9. The method of claim 8 wherein the antagonist comprises an Fc polypeptide fused to: (a) a TWEAK receptor extracellular domain; or (b) a fragment or variant of (a) that is capable of binding TWEAK.
10. The method of claim 9 wherein the TWEAK receptor extracellular domain comprises amino acids 28-79 of SEQ ID NO:7.
11. The method of claim 10 wherein the antagonist comprises amino acids 28-309 of SEQ ID NO:7.
12. The method claim 6 wherein the antagonist comprises an antibody that binds specifically to the TWEAK receptor extracellular domain.
13. The method of claim 12 wherein the antibody is selected from the group consisting of monoclonal antibodies, humanized antibodies, transgenic antibodies, and human antibodies.
14. The method of claim 12 wherein the antibody is conjugated to a radioisotope, to a plant-, fungus-, or bacterial-derived toxin such as ricin A or diphtheria toxin, or to another chemical poison.
15. The method of claim 6 wherein the antagonist disrupts the interaction between the TWEAK receptor and a TRAF molecule.
16. The method of claim 5 wherein the mammal has a disease or condition mediated by angiogenesis.
17. The method of claim 16 wherein the disease or condition is characterized by ocular neovascularization.

18. The method of claim 16 wherein the disease or condition is a solid tumor.

19. The method of claim 16 wherein the method further comprises treating the mammal with radiation.

20. The method of claim 16 wherein the method further comprises treating the mammal with a second chemotherapeutic agent.

21. The method of claim 20 wherein the second chemotherapeutic agent is selected from the group consisting of alkylating agents, antimetabolites, vinca alkaloids and other plant-derived chemotherapeutics, nitrosoureas, antitumor antibiotics, antitumor enzymes, topoisomerase inhibitors, platinum analogs, adrenocortical suppressants, hormones, hormone agonists, hormone antagonists, antibodies, immunotherapeutics, blood cell factors, radiotherapeutics, and biological response modifiers.

22. The method of claim 20 wherein the second chemotherapeutic agent is selected from the group consisting of cisplatin, cyclophosphamide, mechlorethamine, melphalan, bleomycin, carboplatin, fluorouracil, 5-fluorodeoxyuridine, methotrexate, taxol, asparaginase, vincristine, and vinblastine, lymphokines and cytokines such as interleukins, interferons (including alpha, beta, or delta), and TNF, chlorambucil, busulfan, carmustine, lomustine, semustine, streptozocin, dacarbazine, cytarabine, mercaptopurine, thioguanine, vindesine, etoposide, teniposide, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin, mitomycin, L-asparaginase, hydroxyurea, methylhydrazine, mitotane, tamoxifen, and flouxymesterone.

23. The method of claim 20 wherein the second chemotherapeutic agent is selected from the group consisting of Flt3 ligand, CD40 ligand, interleukin-2, interleukin-12, 4-1BB ligand, anti-4-1BB antibodies, TNF antagonists and TNF receptor antagonists, TRAIL, CD148 agonists, VEGF antagonists, VEGF receptor antagonists, and Tek antagonists.

24. A method of promoting angiogenesis according to claim 4 wherein the composition comprises a TWEAK receptor agonist.

25. The method of claim 24 wherein the agonist is an agonistic antibody that binds specifically to the TWEAK receptor extracellular domain.

26. The method of claim 25 wherein the antibody is selected from the group consisting of monoclonal antibodies, humanized antibodies, transgenic antibodies, and human antibodies.

27. The method of claim 25 wherein the agonist is administered:

(a) to treat a vascularization deficiency in cardiac or peripheral tissue, including coronary artery disease, myocardial ischemia, myocardial infarction, angina pectoris, peripheral circulation deficits, limb ischemia/ reperfusion injury;

(b) to enhance wound healing, organ transplantation, reconnection of severed digits or limbs, or vascular or skin grafting; or

(c) in conjunction with bypass surgery or angioplasty.

28. An antagonist comprising:

(a) an Fc polypeptide or leucine zipper domain; and

(b) a TWEAK receptor extracellular domain or fragment or variant thereof that is capable of binding TWEAK.

29. The antagonist of claim 28 wherein the TWEAK receptor extracellular domain comprises amino acids 28-79 of SEQ ID NO:7.

30. The antagonist of claim 28 wherein the antagonist comprises amino acids 28-309 of SEQ ID NO:7.

31. A nucleic acid encoding an antagonist according to claim 28.

32. An expression vector comprising the nucleic acid of claim 31.

33. A recombinant host cell comprising the nucleic acid of claim 31.

34. A method of producing a TWEAK receptor antagonist comprising culturing the host cell of claim 33 under conditions promoting expression of the antagonist.

35. A method of identifying a compound that is capable of modulating angiogenesis comprising:

(a) identifying a test compound that binds to a TWEAK receptor extracellular domain, wherein the test compound is not TWEAK;

(b) identifying a test compound that affects the interaction between a TWEAK and a TWEAK receptor; or

(c) identifying a test compound that modulates the interaction between a TWEAK receptor and a TRAF.

36. The method of claim 35 further comprising determining the ability of the test compound to modulate endothelial cell proliferation and/or endothelial cell migration and/or angiogenesis.

37. The method of claim 35 wherein the modulation is stimulatory.

38. The method of claim 35 wherein the modulation is inhibitory.

39. A method of modulating the binding of TWEAK to the TWEAK receptor in a mammal in need of such treatment, comprising administering to the mammal an inhibition-effective amount of a composition comprising a TWEAK receptor antagonist selected from the group consisting of : (a) a soluble TWEAK receptor extracellular domain; and (b) an antibody that binds to the TWEAK receptor extracellular domain.

40. A method for targeting a detectable label or chemotherapeutic to vascular tissue comprising contacting vascular tissue with an antibody that binds TWEAK receptor.

41. The method of claim 40 wherein the antibody is conjugated to a radioisotope, chemiluminescent or fluorescent compound, or enzyme.

42. The method of claim 40 wherein the antibody is conjugated to a cytotoxin.